REMARKS

A check for $60.00 for a 1-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application during its pendency may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-16 are pending in this application. A Supplemental Information Disclosure Statement and Form PTO-1449 in submitted herewith. A check for $180 for the filing fee is enclosed.

Provided herein are the following supporting documents:

Meyer, "Mucoids and Glycoproteins," in Advances in Protein Chemistry, Vol. II (Anson & Edsall, eds.), pp. 249-275 (1945);

Cheresh *et al.*, J. Biol. Chem. 262(4): 1434-1437 (1987);

Zimrin *et al.*, J. Clin. Invest. 81(5): 1470-1475 (1988);

Rosa *et al.*, J. Biol. Chem. 264(21): 12596-12603 (1989);

Bodary *et al.*, J. Biol. Chem. 265(11): 5938-5941 (1990);

Dedhar *et al.*, J. Cell Biol. 110: 2185-2193 (1990);

Hall *et al.*, J. Cell Biol. 110: 2175-2184 (1990);

Otey *et al.*, J. Cell Biol. 111: 721-729 (1990);

Smith *et al.*, J. Biol. Chem. 265(19): 11008-11013 (1990);

Stamatoglou *et al.*, J. Cell Biol. 111: 2117-2127 (1990);

Tsuji *et al.*, J. Biol. Chem. 265(12): 7016-7021 (1990);

Akiyama *et al.*, J. Neuroimmunol. 32(1): 19-28 (1991);

Elices *et al.*, J. Cell Biol. 112(1): 169-181 (1991);

Goodman *et al.*, J. Cell Biol. 113(4): 931-941 (1991);

Kieffer *et al.*, J. Cell Biol. 113(2): 451-461 (1991);

Ruoslahti, J. Clin. Invest. 87: 1-5 (1991);

Chang *et al.*, Int. J. Cancer 51(3): 445-451 (1992); and

Pignatelli *et al.*, Hum. Pathol. 23:1159-1166 (1992).

REJECTION OF CLAIMS 1-16 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the applicant had possession of the claimed subject matter at the time the application was filed. The Examiner alleges that there is no support in the originally filed claims or specification for detecting β_3 integrin by any means other than by monoclonal antibody binding.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure. 35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (*emphasis in original*).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (*see also*, MPEP 2163.02). An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the

invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

THE CLAIMS

Claim 1 is directed to a method for diagnosing infertility in a mammal that includes the steps of detecting the presence and level of a β_3 integrin subunit in an endometrial sample from the mammal at a plurality of stages of the endometrial cycle; and correlating delayed appearance or a reduced level of β_3 integrin subunit expression with infertility. Claims 2-16 depend from claim 1 and are directed to various embodiments thereof.

ANALYSIS

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d at 265, 191 USPQ at 98. *See also Ex parte Sorenson*, 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987) (*see, also* MPEP 2163.04). In this instance, the Examiner has not provided reasons why skilled persons would not recognize disclosure of what is claimed. Applicant respectfully submits that the skilled artisan would readily glean from the disclosure that the invention lies in discovery of the timing of appearance and level of β_3 in the endometrium and its diagnostic applicability, not in the particular methods or reagents used to detect β_3 in a sample.

MPEP 2163.05 states that the

> failure to meet the written description requirement of 35 U.S.C. 112, first paragraph, commonly arises when the claims are changed after filing to either broaden or narrow the breadth of the claim limitations, or to alter a numerical range limitation or to use claim language which is not synonymous with the terminology used in the original disclosure. To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier filing date or filing date under 35 U.S.C. 119, 120 or 365(c), each claim limitation must be expressly, implicitly or inherently supported in the originally filed disclosure.

Applicant respectfully submits that detecting the presence of a β_3 subunit of integrin in an endometrial sample is expressly supported in the originally filed disclosure. For example, at page 3, lines 1-5, the present specification discloses that:

> Methods of diagnosing fertility and methods of monitoring endometrial maturation in a mammal are also provided by monitoring the appearance of the β_3 subunit of integrin in endometrium from a plurality of stages of the endometrial cycle. This is preferably done with a monoclonal antibody. (emphasis added).

The specification also teaches on page 10, lines 1-14 that:

> The methods for diagnosing infertility and for detecting the window for embryo implantation in the endometrium are also within the scope of the invention. As provided herein, the β_3 subunit of integrin appears at day 20 of the menstrual cycle. It is also provided herein that $\alpha v/\beta_3$ on endometrial epithelium binds fibronectin, vitronectin and osteopontin. These molecules may provide a bridge between the $\alpha v/\beta_3$ integrin of the endometrium and the embryo. Further, patients with luteal phase dysfunction have delayed endometrial maturation, infertility and negative staining for β_3 on days 20 through 24. Thus, the optimal time for fertility may be determined by repetitively testing endometrial samples at a plurality of stages in the menstrual cycle. As such, screening for β_3 provides a method of diagnosing infertility and for detecting the window of embryo implantation in the endometrium (emphasis added).

Further, at page 9, lines 13-17, the specification states that:

> Methods of detecting β_3 in the endometrium include all methods of identifying glycoproteins known in the art. These methods include, but are not limited to, immunohistochemistry techniques such as immunoblotting or Western blotting, immunoperoxidase staining, fluorescein labeling, diaminobenzadine and biotinylation. (emphasis added)

Hence, in this instance, there is no basis to conclude that a person skilled in the art at the time the original application was filed would not have recognized the applicant was in possession of the methods as claimed in view of the disclosure of the application as filed. It is respectfully submitted that the specification teaches that the β_3 integrin in a sample can be detected by any manner, method or reagent including by monoclonal antibody binding. The specification states that methods of detecting β_3 include all methods of identifying glycoproteins known in the art. Therefore, applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant contemplated and was in possession of the subject matter claimed.

Rebuttal to Examiner's Arguments

The Examiner alleges that because the claims do not specify a means by which to detect β_3 integrin, the claims are read to include any means and by any agent to detect β_3 integrin. The Examiner urges that, in reviewing the breadth of applicant's claims, under MPEP 2163.05(I), there is substantial variation within the "genus" defined by the Examiner as the "method of detecting β_3 integrin" and alleges that applicant has not disclosed a sufficient number of species representative of the entire genus.

Applicant agrees that the claims are directed to diagnostic methods in which β_3 integrin in a sample is detected by any method and any reagent. None of the claims are directed to methods of detecting β_3 integrin *per se*. The pending claims are directed to methods for diagnosing infertility in a mammal. The claims include as an element detecting β_3 integrin in an endometrial sample.

Applicant respectfully submits that the characterization of the recitation "detecting β_3 integrin" in the claims as a claimed "genus" is incorrect. "Detecting β_3 integrin" is not a genus that encompasses the claimed subject matter. A novelty defeating disclosure with respect to a particular method or reagent for detecting β_3 integrin in a sample would not necessarily anticipate a claim to a method for diagnosing infertility in a mammal.

In this instance, the claimed methods would not be anticipated by a disclosure of a particular method or reagent for detecting β_3 integrin in a sample because anticipation requires disclosure in a single reference of every claimed element. Applicant respectfully submits that an inventive concept of the claimed subject matter lies in discovery of the timing of the appearance of β_3 in an endometrial sample and its diagnostic applicability, not in the particular methods or reagents used to detect β_3 integrin in a sample. A disclosure of a particular method or reagent for detecting β_3 integrin in a sample does not disclose that the timing of the appearance of β_3 in an endometrial sample correlates with certain events.

For example, a reference disclosing detecting β_3 integrin in a sample, for example, using polyclonal antibodies to detect β_3 integrin in a brain tissue sample, does not anticipate the claims to a method for diagnosing infertility in a mammal, nor does it necessarily render such method claims obvious. Therefore, because a novelty defeating disclosure with respect to a particular method or reagent for detecting β_3 integrin in a sample would not anticipate the claimed methods, the element "detecting β_3 integrin" is not a genus that encompasses the claimed subject matter.

What the Examiner has characterized as a "genus" is routine testing reagents and methods known to the skilled artisan at the time of filing of the original application. Analysis and detection of glycoproteins is routine in the art and has been practiced for over 50 years (for example, see Meyer, "Mucoids and Glycoproteins" in *Advances in Protein Chemistry*, Vol. 2 (1945), pages 249-273). Methods for detecting subunits of integrin were known in the art at the time of the filing of the original application. For example, see:

Cheresh *et al.*, **J. Biol. Chem.** 262(4): 1434-1437 (1987)
Zimrin *et al.*, **J. Clin. Invest.** 81(5): 1470-1475 (1988)
Rosa *et al.*, **J. Biol. Chem.** 264(21): 12596-12603 (1989)
Bodary *et al.*, **J. Biol. Chem.** 265(11): 5938-5941 (1990)
Tsuji *et al.*, **J. Biol. Chem.** 265(12): 7016-7021 (1990)
Hall *et al.*, **J. Cell Biol.** 110: 2175-2184 (1990)
Dedhar *et al.*, **J. Cell Biol.** 110: 2185-2193 (1990)
Smith *et al.*, **J. Biol. Chem.** 265(19): 11008-11013 (1990)
Otey *et al.*, **J. Cell Biol.** 111: 721-729 (1990)
Stamatoglou *et al.*, **J. Cell Biol.** 111: 2117-2127 (1990)
Ruoslahti, **J. Clin. Invest.** 87: 1-5 (1991)
Elices *et al.*, **J. Cell Biol.** 112(1): 169-181 (1991)
Kieffer *et al.*, **J. Cell Biol.** 113(2): 451-461 (1991)
Goodman *et al.*, **J. Cell Biol.** 113(4): 931-941 (1991)
Akiyama *et al.*, **J. Neuroimmunol.** 32(1): 19-28 (1991)
Chang *et al.*, **Int. J. Cancer** 51(3): 445-451 (1992)
Pignatelli *et al.*, **Human Pathol.** 23(10): 1159-1166 (1992)

These references are representative of the numerous publications directed to detection of proteins in general, and to the subunits of integrin in particular. The references evidence that the knowledge of those of skill in the art is extensive and that methods and reagents for detecting β_3 integrin in a sample were well known by 1992.

Representative Number of Species

Even if the characterization of detecting β_3 integrin in an endometrial sample as a genus is correct, which the applicant does not admit (and which, as discussed above, applicant urges is incorrect), applicant respectfully submits that the written description requirement is satisfied. MPEP 2163.05(I) states that the

> Written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The analysis for compliance with the written description requirement where claims are directed to a genus includes determining whether there a representative number of examples

explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species. Applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied.

The specification explicitly discloses a number of methods and reagents for detecting β_3 integrin in a sample. For example, the specification discloses using a monoclonal antibody as an exemplary method for detecting β_3 integrin in a sample. The specification further explicitly discloses detecting β_3 integrin in a sample by immunoblotting, Western blotting, immuno-peroxidase staining, fluorescein labeling, diaminobenzadine and biotinylation (see page 9, lines 14-17). The specification also explicitly discloses detecting β_3 integrin in a sample by electrophoresis (see page 5, lines 12-24 and page 19, lines 3-6). Thus, the specification explicitly discloses at least seven methods or reagents for detecting β_3 integrin in a sample.

The specification implicitly discloses other methods or reagents for detecting β_3 integrin in a sample. For example, the specification discloses using all methods of identifying glyco-proteins known in the art (*e.g.*, see page 9, lines 13-14). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). Applicant respectfully submits that detection of glycoproteins was well known in the art at the time of filing of the original application. Further, applicant submits that various reagents and methods for detecting β_3 integrin in a sample in addition to monoclonal antibodies were known in the art at the time of filing the original application. Akiyama *et al.* teaches using polyclonal antibodies in immunochemical assays for detecting β_3 integrin in brain tissue (J Neuroimmunol. 32(1): 19-28 (April 1991). Pignatelli *et al.* discloses a immunochemical study for integrins and their accessory adhesion molecules (Hum. Pathol. 23(10): 1159-66 (October 1992). Smith *et al.* (J. Biol. Chem. 265(10): 11008-13 (July 1990)) discloses a number of techniques for analysis of and discrimination between β_3 integrin and β_5, including Western blot analysis, ligand-binding assays, radioiodination, immunoprecipitation using polyclonal antibody assays, peptide mapping and amino-terminal acid sequencing. Zimrin *et al.* discloses northern blot analysis of human β subunit GPIIIa, which is renamed as β_3 integrin (see Zimrin *et al.*, J. Clin. Invest. 81(5): 1470-75 (1988).

Thus, the specification provides a representative number of examples explicitly and implicitly and teaches that methods of detecting β_3 integrin include all methods of identifying glycoproteins known in the art. Hence, those of skill in the art would recognize as a common

element among members of the "genus" the ability of the method or reagent to detect a particular protein in a sample. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

One Species Adequately Supports the "Genus"

In addition, applicant respectfully directs the Examiner's attention to MPEP 2163.05. which states, in part, that:

> On the other hand, there may be situations where one species adequately supports a genus. *See,* e.g., *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 3232, 326-27 (CCPA 1981) (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered).

The instant situation is analogous to the issues addressed in *In re Rasmussen*. As discussed above, methods and reagents for detecting β_3 integrin in a sample were known to the skilled artisan and were routine in this art at the time of the filing of the original application. The instant claims are directed to methods for diagnosing infertility in a mammal. The claims are directed to diagnostic methods in which β_3 integrin in a sample is detected by any method and any reagent. The selection of a particular method or reagent by which β_3 integrin in the sample is detected is not critical. Applicant respectfully submits that the skilled artisan would readily conclude from the disclosure that an inventive concept of the claimed subject matter lies in discovery of the timing of appearance of β_3 in the endometrium and its diagnostic applicability, not in the particular methods or reagents used to detect β_3 in a sample. Hence, in the instant claims, one skilled in the art reading the specification would understand that it is unimportant **how** the β_3 integrin is detected in a sample, **so long as it is detected**.

As discussed above, the instant application explicitly discloses at least seven methods of detecting β_3 integrin and, as demonstrated by the publications cited above and previously made of record, those of skill in the art can readily detect β_3 integrin in a sample. Thus, applying the reasoning used in *In re Rasmussen*, because it is unimportant how the β_3 integrin is detected in the sample, disclosure of a single method of detection adequately supports the "genus" in the instant claims. If disclosure of a single genus adequately supports the "genus" under the rationale applied in *In re Rasmussen*, then certainly the disclosure of seven methods of detecting

β_3 integrin in a sample in the instant application adequately supports the claimed "genus." Therefore, using the rationale applied in *In re Rasmussen*, because one skilled in the art reading the specification would understand that it is unimportant how the β_3 integrin in a sample is detected, and because the application discloses at least seven methods of detecting β_3 integrin in a sample, applicant respectfully submits that the disclosure in the application adequately supports the "genus" of detecting β_3 integrin in a sample.

REJECTION OF CLAIMS 1-16 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH - Enablement

Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, because it is alleged that the specification, while being enabling for detecting β_3 in a sample using monoclonal antibodies, does not reasonably provide enablement for detecting β_3 integrin in a sample by *any* means. The Examiner states that the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the invention commensurate in scope with these claims. This rejection is traversed.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *See, Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

ANALYSIS

Applying the above-noted factors to the instant facts reveals that the amount of experimentation is not undue.

1. The scope of the claims.

Claim 1 is directed to a method for diagnosing infertility in a mammal that includes the steps of detecting the presence and level of a β_3 integrin subunit in an endometrial sample from the mammal at a plurality of stages of the endometrial cycle and correlating delayed appearance or a reduced level of the β_3 integrin subunit expression with infertility.

Thus, the scope of the claims is identical to the scope of the discovery of the applicant, *i.e.*, that the timing of the appearance of β_3 in the endometrium correlates with certain events. The skilled artisan would readily conclude from the disclosure that an inventive concept lies in discovery of the timing of the appearance of β_3 in the endometrium and its diagnostic applicability, not in the particular reagents used to detect β_3 integrin in a sample. For example, see page 10, lines 1-17; page 12, lines 1-9; and page 19, lines 12-14.

2. Level of skill in the art

In this instance, the level of skill in the art is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

3. The amount of direction or guidance presented and the presence or absence of working examples.

The specification provides a general description of an observation that the timing of the appearance of β_3 in the endometrium is indicative of fertility, uterine receptivity and endometrial maturation and that detection of β_3 integrin in an endometrial sample can be used to assess these events and conditions. This is a broad observation. The specification then provides a working example to show that this correlation is correct, and uses a monoclonal antibody as an exemplary method for detecting the presence of the protein in a sample. The specification does not state in any manner that the method or reagent used for detection of β_3 integrin in a sample should be limited to that which is exemplified, and in fact states that <u>any</u> method known in the art can be used (for example, see page 9, lines 13-14).

The requirements of 35 U.S.C. §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973) :

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

Hence there is no requirement for the applicant to exemplify or even provide an example of everything within the scope of the claims. The Patent Office cannot "limit all claims to the specific examples, notwithstanding the disclosure of a broader invention."

4. The nature of the invention; state of the art and the predictability of the art.

The claims are based on the observation of a correlation between the timing of the appearance of β_3 integrin in the endometrium and certain events and conditions. As noted above, the application discloses that the β_3 integrin subunit appears in the endometrium at particular time periods in a way that can be correlated with certain events and used diagnostically by detecting β_3 integrin in an endometrial sample. This is a general observation, and there is no showing in the specification or by the Office that this observation is impacted by the manner in which the presence of β_3 integrin in an endometrial sample is detected. The "invention" is not the discovery that β_3 can be detected with a monoclonal antibody. Detecting β_3 integrin in a sample can be effected by any method or reagent known to the skilled artisan. This is routine detection of a glycoprotein.

Applicant respectfully submits that, in 1992, the state of the art of protein detection in a sample was advanced. Many protein detection methods (such as polyclonal antibodies, sequencing, gel electrophoresis, and mass spectrometry) were perfected and used from at the very least the mid 1970's. By 1992, these methods were routine and yield predictable results.

The specification states that detection with a monoclonal antibody is an exemplary method to detect β_3 integrin (page 3, lines 1-5):

> Methods of diagnosing fertility and methods of monitoring endometrial maturation in a mammal are also provided by monitoring the appearance of the β_3 subunit of integrin in endometrium from a plurality of stages of the endometrial cycle. This is preferably done with a monoclonal antibody.

The language "preferably" evidences that applicant contemplated detecting by other methods or reagents. This conclusion is supported by the language that β_3 integrin can be

detected by any method for detecting glycoproteins known to the skilled artisan. For example, the specification teaches on page 9, lines 13-17 that:

> Methods of detecting β_3 in the endometrium **include all methods of identifying glycoproteins known in the art**. These methods include, but are not limited to, immunohistochemistry techniques such as immunoblotting or Western blotting, immunoperoxidase staining, fluorescein labeling, diaminobenzadine and biotinylation. [*emphasis added*]

Thus, the manner in which β_3 integrin in a sample is detected should not be a limitation on the claims. At the time of filing of the original application, those of skill in the art, once apprised of the correlation between the timing of the presence of β_3 integrin and certain events, could then detect its presence in a sample by any of a variety of methods for detection of proteins.

As discussed above, various methods and reagents for detecting a particular protein, and in particular integrin subunits, were available at the time of filing the original application. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). A skilled artisan would have known that methods and reagents in addition to the disclosed exemplary monoclonal antibodies and electrophoresis techniques could be used to detect the protein. For example, Akiyama *et al.* teaches using polyclonal antibodies in immunohistochemical assays for localization of β_3 integrin in Alzheimer brain tissue (J Neuroimmunol. 32(1): 19-28 (April 1991). Rosa *et al.* discloses structural features of the β subunit of integrin using polyclonal antibodies, electrophoresis and immunoprecipitation (J. Biol. Chem. 264(21): 12596-603 (July 1989). Smith *et al.* (J. Biol. Chem. 265(10): 11008-13 (July 1990)) discloses a number of techniques for analysis of and discrimination between β_3 integrin and β_5 integrin, including Western blot analysis, solid phase ligand-binding assays, radioiodination, immunoprecipitation using polyclonal antibody assays, peptide mapping and amino-terminal acid sequencing.

The protein can be assayed according to its physical or chemical properties, *e.g.*, molecular weight, charge, or polarity, etc. The protein can also be assayed according to its biological activity such as specific binding to its biological binding partner, catalytic activities or ability to induce or suppress physiological reactions in target cells. Expression can be detected at the RNA level, *i.e.*, by assaying the production of the mRNA. For example, Zimrin *et al.* discloses northern blot analysis of human β subunit GPIIIa, renamed as β_3 integrin (see Zimrin *et al.*, J. Clin. Invest. 81(5): 1470-75 (1988). Thus, methods that do not rely on the use of monoclonal antibodies for detecting β_3 integrin were available and known to skilled artisans at the time of filing the original application.

5. The quantity of experimentation.

There is nothing of record to suggest that detection of the presence β_3 in a sample by, for example, gel electrophoresis or using polyclonal antibodies, would require development of new procedures or any experimentation. Such methods have been used since at least the late 1970's and are not difficult to adapt for detection of different proteins. For example, an endometrial sample that contains β_3 integrin could be run side-by-side with the test sample. The absence of a band in the test sample at a molecular weight corresponding to the molecular weight of β_3 integrin would indicate the sample did not contain β_3 integrin at that particular testing interval. A reduced intensity of a band in the test sample at a molecular weight corresponding to the molecular weight of β3 integrin would indicate the sample contained a reduced level of β3 integrin. As discussed above, published methods of using, for example, electrophoretic methods and polyclonal antibodies to detect β_3 integrin in a sample, where known at time of filing the original application.

For illustration only, it is submitted that as of the earliest filing date of the priority application for the present application, the skilled artisan could have detected β_3 integrin in a sample using Northern blot analysis without any undue experimentation. First, by 1992, the standard procedure for carrying out a Northern blot analysis was well known in the art (see *e.g.*, Sambrook *et al.*, Molecular Cloning A Laboratory Manual (2nd ed.), Cold Spring Harbor Laboratory Press (1989), 7.39-7.57). In addition, β_3 integrin gene sequences were publicly available. In a reference published in 1988, Zimrin *et al.* disclosed the cDNA sequence of human β subunit GPIIIa (β_3 integrin) (see Zimrin *et al.*, J. Clin. Invest. 81(5): 1470-75 (1988). Hence, probes to be used in the Northern blot analysis of β_3 integrin can be designed according to the published β_3 integrin sequence. Further, in a reference published on May 28, 1992, Chang *et al.* demonstrated that β_3 integrin in a sample can be detected and analyzed by Northern blotting analysis (see Chang *et al.*, Int. J. Cancer 51(3): 445-51 (1992)). Thus, methods that do not rely on monoclonal antibodies for detecting β_3 integrin in a sample were available and known to skilled artisans at the time of filing the original application.

6. Predictability

As discussed above, the level of knowledge and skill in the preparation, isolation, manipulation and detection of integrin, its subunits and related proteins was high as of the effective filing date of the instant application. Therefore, given the teachings of the specification, in combination with what was known at the time the original application was

filed, applicant respectfully submits that β_3 integrin can be detected in a sample predictably using any methods that are known to those skilled in this art.

CONCLUSION

The essence of the subject matter claimed in the present application is the recognition that the timing of the β_3 appearance in the endometrium is correlated with certain events, such as infertility. The manner in which β_3 integrin is detected in an endometrial sample is independent of the correlation with the events, and cannot be a limitation on the claims. At the time of filing of the original application, those of skill in the art, once apprised of the correlation between the timing of the appearance of β_3 integrin in the endometrium and certain events, could then detect its presence or absence in a sample by any of a variety of methods for detection of a glycoprotein in a sample.

Various methods for detecting a particular glycoprotein, and in particular β_3 integrin, were available at the time of filing the original application. For example, polyclonal antibodies can be used to detect β_3 integrin. The β_3 integrin protein can be assayed according to its physical or chemical properties, *e.g.*, molecular weight, charge, or polarity, and detected, for example, by gel electrophoresis or mass spectrometry. The protein can also be assayed according to its biological activity such as specific binding to its biological binding partner, catalytic activities or ability to induce or suppress physiological reactions in target cells. The protein can further be assayed according to its immunological properties, *e.g.*, specific binding to its antibody.

In light of the scope of the claims, the teachings in the specification, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation for a person skilled in the art to detect β_3 integrin in an endometrial sample using methods or reagents other than the exemplary monoclonal antibodies. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Policy Considerations

The Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. Moreover, it is unfair, unduly limiting and contrary to the public policy and constitutional

mandate that underlie the U.S. patent system to require applicant to limit the instant claims to the use of monoclonal antibodies for detection of the presence of β_3 integrin is a sample. To do so permits one of skill in this art to practice the disclosed invention but avoid liability for infringement merely by detecting β_3 integrin in a sample using, *e.g.*, electrophoresis.

As a broad body of knowledge is available in the area of biochemistry in the preparation of assays for the detection of glycoproteins, such as β_3 integrin, it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to a particular detection method or reagent. See, e.g., *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. If applicant is required to limit the claims to detection of β_3 integrin in a sample using only monoclonal antibody binding, then those of skill in the art could by virtue of the teachings of this application readily practice what is claimed by detecting β_3 integrin in a sample using another known method of detection, but avoid infringing such limited claims. To permit that is simply not fair. As noted above, the "invention" is the discovery that the β_3 integrin subunit appears in the endometrium at particular time periods in a way that can be correlated with certain events and used diagnostically. Further, the instant application in light of the knowledge of those of skill in the art provides adequate guidance for the diagnostic use of this correlation. Having done so, it is now routine for others to detect β_3 integrin by any method known in this art. Those of skill in the art should not be permitted to make such minor modifications by substituting a detection method other than monoclonal antibody binding and avoid infringing such claims.

REJECTION OF CLAIMS 1-16 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being incomplete method claims because an essential step of the method is not recited. The

Examiner alleges failure of claims 1-14 to recite an agent to detect the β_3 integrin subunit makes all the claims indefinite. The Examiner suggests incorporating the detection methods listed in claims 15 and 16 into the base claim to overcome the rejection.

This rejection is respectfully traversed.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an Applicant is entitled to be its own lexicographer (see, e.g., MPEP 2111.01). The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); *See, also, Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed.Cir. 1997). The words of a claim must be given their plain meaning unless applicant has provided a clear definition in the specification. *In re Zletz*, 893,

F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed.Cir. 1989). The claims are definite if they "make clear what subject matter they encompass and thus what the patent precludes others from doing." *In re Spiller*, 182 USPQ 614 (CCPA 1974).

THE CLAIMS

Claim 1 is directed to a method for diagnosing infertility in a mammal that includes the steps of detecting the presence and level of a β_3 integrin subunit in an endometrial sample of a mammal at a plurality of stages of the endometrial cycle and correlating delayed appearance or a reduced level of β_3 integrin subunit expression with infertility. Claims 2-16 depend from claim 1 and are directed to various embodiments thereof.

ANALYSIS

As a preliminary matter, applicant respectfully submits that the rejection as applied to claims 15 and 16 is in error. In the Action, the Examiner states that claims 15 and 16 include detection methods, and suggests that incorporation of the detection methods listed in claims 15 and 16 into the base claim would help to obviate the rejection (see page 6, last two sentences). Thus, claims 15 and 16 include detection methods. Therefore, applicant respectfully requests that the rejection as applied to claims 15 and 16 be withdrawn.

As applied to claims 1-14, applicant respectfully submits that the rejection is without merit. As noted above, definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The instant claims are definite because the steps of (i) detecting β_3 integrin subunit in an endometrial sample and (ii) correlating delayed appearance or a reduced level of β_3 integrin subunit expression with infertility, adequately define the metes and bounds of the claimed subject matter in light of the disclosure in the specification and what is known to those of skill in the art.

As discussed above in the traverse of the enablement rejection, methods of detecting β_3 integrin in a sample are provided throughout the specification. For example, the specification discloses using a monoclonal antibody as an exemplary method of detection of β_3 integrin (page 3, lines 4-5 and page 8, lines 21-32). Further, the specification discloses alternate methods for detecting β_3 integrin, such as using electrophoresis to detect β_3 integrin by its molecular weight (see page 5, lines 22-24). In addition, other methods and reagents are specifically contemplated in the disclosure. For example, the specification teaches on page 9, lines 13-17 that:

> Methods of detecting β_3 in the endometrium include all methods of identifying glycoproteins known in the art. These methods include, but are not limited to, immunohistochemistry techniques such as immunoblotting or Western blotting, immunoperoxidase staining, fluorescein labeling, diaminobenzadine and biotinylation.

Furthermore, as discussed above in addressing the rejection for alleged lack of enablement, methods for detecting β_3 integrin were well known in the art at the time of filing of the above-captioned application and as of its earliest priority date. As of the earliest priority date of the above-captioned application, those of skill in the art knew several methods of detecting β_3 integrin that do not require monoclonal antibody binding. For example, Akiyama *et al.* teaches using polyclonal antibodies in immunohistochemical assays for localization of β_3 integrin in Alzheimer brain tissue (J Neuroimmunol. 32(1): 19-28 (1991)). Bodary *et al.* teaches immuno-precipitation using polyclonal antibodies and electrophoresis for distinguishing between the α and β subunits of integrin (J. Biol. Chem., 265(11): 5938-5941 (1990)). Dedhar *et al.* teaches ligand specific affinity chromatography techniques to detect the α and β subunits of integrin (J. Cell Biol. 110:2185-2193 (1990)). Zimrin *et al.* discloses northern blot analysis of β_3 integrin (see Zimrin *et al.*, J. Clin. Invest. 81(5): 1470-75 (1988). Smith *et al.* discloses a number of techniques for analysis of and discrimination between β_3 integrin and β_5 integrin, including Western blot analysis, solid phase ligand-binding assays, radioiodination, immunoprecipitation using polyclonal antibody assays, peptide mapping and amino-terminal acid sequencing.

Therefore, it is respectfully submitted that one of skill in the art, given the methods as instantly claimed, would recognize (i) the scope/boundaries of the claimed subject matter; and (ii) the various techniques by which the β_3 integrin subunit can be detected in an endometrial sample. No further elaboration is necessary to render definite each of the steps of the claimed method. It is respectfully submitted that in this instance, the claims reasonably apprise the skilled artisan of the scope and utilization of the claimed methods. Therefore, it is respectfully submitted that independent claim 1 and claims dependent thereon are not indefinite.

REJECTION OF CLAIMS 1-16 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 3, 4, 14-19 and 28 of U.S. Patent No. 6,733,979 because, although the conflicting claims are not identical, they are allegedly not patently distinct from each other because instant claims 1-6 and 14-22 are broader in scope and would encompass claims 3, 4, 14-19 and 28 of U.S. Patent No. 6,733,979.

It is noted that issues of double patenting cannot be resolved until there are allowable claims in the application. Applicant respectfully requests deferral of this issue until an indication that there is allowable subject matter in the instant application. Until that time, the propriety of the rejection cannot be properly assessed. Upon review of the claims pending at the time, the need for a Terminal Disclaimer will be assessed, and, if needed, a Terminal Disclaimer will be provided.

PROVISIONAL REJECTION OF CLAIMS 1-16 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 5,279,941. It is alleged in the Office Action that although the conflicting claims are not identical, they allegedly are not patently distinct because the claims of U.S. Patent No. 5,279,941 are species claims to the instantly pending claims and therefore allegedly anticipate them.

Since obviousness-type double patenting cannot be assessed until there is allowable subject matter, applicant respectfully requests deferral of this issue until an indication that there is allowable subject matter in the instant application. Until that time, the propriety of the rejection cannot be properly assessed. Upon review of the claims pending at the time, the need for a Terminal Disclaimer will be assessed, and, if needed, a Terminal Disclaimer will be provided.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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